

# **DNA Based Damage: A Car-Parrinello Molecular Dynamics Study of Guanine and Thymine with an OH Radical**

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**DNA base damage: A Car-Parrinello Molecular Dynamics Study of  
Guanine and Thymine with an OH Radical**

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The Car-Parrinello molecular dynamics<sup>1</sup> (CPMD) method has proven itself to be one of the most successful techniques in elucidating important chemical phenomena. CPMD obtains the forces on the atoms by using potentials based in the Kohn-Sham formulation of density functional theory. The efficiency of the CPMD method lies in the fact that it treats the electronic degrees of freedom classically by introducing a fictitious mass. The resulting scheme is a very stable molecular dynamics method where the forces on the atoms are derived from first principles. One advantage to using this kind of methodology is that one can see bond breaking and bond formation as a species travels along a reacting trajectory. Although CPMD has seen widespread use in materials science, chemistry, and condensed matter physics, it is starting to find its way into biology. Of particular interest is to understand the basic chemistry of radicals and DNA bases in an attempt to characterizing the potential oxidative damage to DNA. It is known that a large endogenous source of oxidizing agents within the cell can lead to the formation of hydroxyl radicals. Thus, it is of interest experimentally to characterize the initial phases of DNA base oxidation induced by an OH radical<sup>2</sup>. The chemical level understanding of such damage has far reaching implications for radiation therapy, health effects of radiation exposure, and aging. Although there are numerous experimental studies on the initial phases of DNA base oxidation, there are still open questions as to the precise mechanisms.

In a previous study we performed an exhaustive study of the possible chemical reactions that can occur when guanine interacts with an OH radical in the gas phase<sup>3</sup>. Guanine was chosen because it is known to have the highest propensity of all the DNA bases for undergoing oxidation. In order to underpin our findings we made direct contact

with traditional static quantum chemical methods. Although traditional quantum chemical methods will not perform finite temperature molecular dynamics, their utility lies in that they are extremely accurate. Thus, using CPMD in conjunction with traditional methods allows one to validate the approximations that are widely used in plane-wave pseudopotential codes (*e.g.* CPMD) that afford one the efficient molecular dynamics implementation. In our previous study with guanine we were able to elucidate different mechanisms leading DNA base damage in the gas phase<sup>3</sup>. This was accomplished with the aid of maximally localized Wannier centroids (WC)<sup>4</sup>. The WC's allow one to track both the nuclear and electronic degrees of freedom separately. One reaction mechanism that was predicted was a hydrogen atom transfer from the guanine to the OH radical yielding water and a guanine cation radical. The second was that we observed partial electron transfer from the guanine to the OH radical followed by proton transfer to form the guanine cation and water. Through the WC analysis it is important to note that both of the aforementioned mechanisms were subject to pi-electron loss from the guanine. It is also interesting to note that the electron transfer could not be determined *a priori* from the static quantum chemical calculations because the reactants and products were treated as isolated subunits. However, when the reacting CPMD trajectory was used as input to the static quantum chemical methods, the partial charge transfer mechanism was corroborated. The results of the aforementioned study pointed to dehydrogenation as being the most free-energetically favorable reaction path. However, this was in disagreement with experimental finding which indicated that a hydroxylated guanine radical was stable intermediate<sup>2</sup>. It should be pointed out that all experiments were conducted at ambient conditions with water as the solvent. Thus the

effects of solvation need to be included in order to make closer contact with experimentally observed mechanisms. To this end, we considered the affects of explicit solvent on the initial phases of oxidative damage in DNA bases.

Although thymine is known not to oxidize as readily as guanine, it has still been implicated as having a key role in DNA base damage. Because of this there are experiments performed to elucidate the products of thymine subjected to an oxidizing agent. It has also been conjectured that the initial phases of thymine damage occur by a different electronic mechanism<sup>5</sup>. We first examined all possible reactions of thymine with an OH radical in the gas phase with both CPMD and static quantum chemical mechanisms. The resulting trends seem to be in good agreement. It is interesting to note that our preliminary data does predict a different reaction mechanism for the initial stages of DNA base oxidation. Through WC analysis we find that sigma-electron loss is responsible for the hydrogen atom transfer to form a thymine cation radical and water. We also performed reactions of the aforementioned DNA bases in the presence of explicit water. Our results here will be discussed as well as a comparison to calculations performed with static quantum chemical solvent models. This work was performed under the auspices of the U.S. Department of Energy by University of California Lawrence Livermore National Laboratory under contract No. W-7405-Eng-48.

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